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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIMECROLIMUS FOAM COMPOSITION CONTAINING HEXYLENE GLYCOL, OPTIONALLY OLEYL ALCOHOL, DIMETHYLISOSORBIDE AND/OR MEDIUM CHAIN TRIGLYCERIDES

(57) Abstract: Pharmaceutical foam compositions substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of: i) hexylene glycol; ii) optionally oleyl alcohol; and iii) dimethylisosorbide and/or medium chain triglycerides; and additionally: iv) when oleyl alcohol is absent, water in an amount of less than 25 %; v) at least one consistency agent; vi) at least one preservative; and vii) at least one surfactant/emulgator; and propellant gas for foaming; and optionally further conventional excipients. They are indicated for use in the treatment of various skin, nail and mucosal diseases.

WO 2005/097068 A1

PIMECROLIMUS FOAM COMPOSITION CONTAINING HEXYLENE GLYCOL, OPTIONALLY OLEYL ALCOHOL, DIMETHYLISOSORBIDE AND/OR MEDIUM CHAIN TRIGLYCERIDES

The invention relates to pharmaceutical compositions, for use in particular in the treatment of skin diseases. It concerns a **pharmaceutical composition comprising the anti-inflammatory ascomycin derivative pimecrolimus in the form of a foam.**

WO 2004/016289 discloses topical pharmaceutical compositions substantially free of ethanol and water which comprise an ascomycin in a carrier vehicle comprising a 3-component mixture amounting to at least 40 % of the total weight of the compositions and consisting of:

i) a C_{3-8} alkanol and/or C_{1-8} alkanediol;

ii) a fatty alcohol; and

iii) a further solvent selected from:

a) an alkane carboxylic acid alkyl ester and/or alkane dicarboxylic acid alkyl ester and/or

b) a hydrophilic co-component and/or

c) a triglyceride;

and optionally further conventional excipients.

While these compositions are essentially single-phase liquid or semi-solid, it is also envisaged in that disclosure that the liquid phase may form the liquid component of a foam formulation.

It has now been found that, surprisingly, foams comprising the ascomycin pimecrolimus in a particular type of formulation not disclosed as such therein and having a high oil content, while optionally including a small amount of added water, are particularly beneficial.

Specifically, the invention concerns a **pharmaceutical foam composition** substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i) hexylene glycol;

ii) optionally oleyl alcohol; and

iii) dimethylisosorbide and/or medium chain triglycerides;

and additionally:

iv) when oleyl alcohol is absent, water in an amount of less than 25 %;

v) at least one consistency agent;

vi) at least one preservative; and

vii) at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients;

hereinafter briefly named "**the composition of the invention**".

Thus at least 40 % of the total weight of the composition is consisting of hexylene glycol, oleyl alcohol, dimethylisosorbide and/or medium chain triglycerides.

In a **subgroup** the composition of the invention is substantially free of ethanol and water and comprises pimecrolimus in a carrier vehicle comprising a 3-component mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i') hexylene glycol;

ii') oleyl alcohol; and

iii') dimethylisosorbide and medium chain triglycerides;

and additionally:

v') at least one consistency agent;

vi') at least one preservative; and

vii') at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients.

In a preferred subgroup thereof the carrier vehicle for pimecrolimus is consisting of:

i') hexylene glycol;

ii') oleyl alcohol; and

iii') dimethylisosorbide and medium chain triglycerides;

and additionally:

v') hydroxypropyl cellulose and/or stearyl alcohol;

vi') p-hydroxybenzoic acid ester with ethyleneglycol phenylether; and

vii') glyceryl monostearate and non-ionic sugar esters; and propellant gas for foaming.

In **another subgroup** the composition of the invention is substantially free of ethanol and comprises pimecrolimus in a carrier vehicle comprising a 2-component mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i") hexylene glycol; and

iii") dimethylisosorbide and/or medium chain triglycerides;

and additionally:

iv") water in an amount of less than 25 %;

v") at least one consistency agent;

vi") at least one preservative; and

vii") at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients.

In a preferred subgroup thereof the carrier vehicle for pimecrolimus is consisting of:

i") hexylene glycol; and

iii") medium chain triglycerides and optionally dimethylisosorbide;

and additionally:

iv") water in an amount of less than 25 %;

v") polyvinylpyrrolidone and stearyl alcohol;

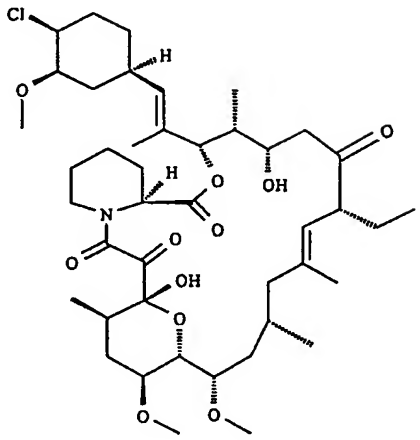
vi") p-hydroxybenzoic acid ester with ethyleneglycol phenylether; and

vii") glyceryl monostearate and lecithin; and propellant gas for foaming.

The composition of the invention is effective independently of the condition of the skin, nail or mucosa, is well tolerated, stable and has particularly interesting penetration properties.

It retains and improves on the beneficial penetration properties of more complex or inhomogenous formulations such as water- or hydrocarbon-based emulsions or suspensions, while being particularly convenient in terms of ease of administration and patient compliance. It has the advantage of consisting of few components, is straightforward to prepare and well-tolerated on human skin.

Pimecrolimus is the compound of formula I



(Example 66a in EP 427680),

i.e. {[1E-(1R,3R,4S)]1R,9S,12S,13R, 14S,17R,18E, 21S,23S,24R,25S,27R}-12-[2-(4-chloro-3-methoxycyclohexyl)-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28,dioxa-4-azatricyclo [22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetraone.

Hexylene glycol preferably is in an amount of from about 1 % to about 10 % when component ii) is present, and preferably in an amount of from about 2 % to about 20 %, preferably from about 5 % to about 10 % when component iv) is present.

Oleyl alcohol when present preferably is in an amount of from about 1 % to about 20 %.

Added **water** when present preferably is in an amount of from about 1 % to about 20 %, especially from about 5 % to about 15 %.

Dimethylisosorbide preferably is in an amount of from about 35 % to about 90 % when component ii) is present, and from about 0 % to about 20 %, preferably from about 0 % to about 10 % when component iv) is present.

Medium chain triglycerides preferably are in an amount of from about 5 % to about 20 % when component ii) is present, and from about 50 % to about 80 %, preferably from about 60 % to about 70 % when component iv) is present.

Consistency agents may be conventional, e.g. as disclosed in WO 2004/016289. They preferably are hydroxypropyl cellulose or polyvinylpyrrolidone, and/or stearyl alcohol; when component ii) is present, they preferably are in an amount of from about 0.1 % to about 5 %, e.g. hydroxypropyl cellulose from about 0.2 % to about 1 % together with stearyl alcohol from

about 1 % to about 5 %; when component iv) is present, they preferably are in an amount of from about 1 % to about 10 %, e.g. polyvinylpyrrolidone from about 1 % to about 5 % together with stearyl alcohol from about 3 % to about 10 %.

Preservatives may be conventional, e.g as disclosed in WO 2004/016289, preferably they are p-hydroxybenzoic acid esters (parabens), e.g. a p-hydroxybenzoic acid ester with ethyleneglycol phenylether, such as Phenonip^R. They preferably are in an amount of from about 0.1 % to about 0.5 %.

Surfactants/emulgators for foaming may be conventional, e.g. cationic, non-ionic or anionic, e.g. cetrimide, lecithin, soaps and silicones. Commercially available surfactants such as Tween^R are also suitable. Preferred are glyceryl monostearate, lecithin and non-ionic sugar esters, such as Sisterna SP-30 and SP-70. When component ii) is present, the amount of surfactant/emulgator is from about 0.5 % to about 5 %, e.g. glyceryl monostearate from about 1 % to about 3 %, together with Sisterna SP-30 and SP-70, each from about 0.5 % to about 2 %. When component iv) is present, the amount of surfactant/emulgator is from about 0.5 % to about 20 %, e.g. glyceryl monostearate from about 1 % to about 3 %, together with lecithin from about 5 % to about 20 %.

The **propellant gas** for foaming is e.g. any harmless gas conventionally used as a propellant, such as butane or propane, or a mixture of butane and propane, e.g. in the ratio about 80/20.

"Substantially free of ethanol" and "substantially free of water" means that neither ethanol nor, respectively, water is added as an intentional constituent part of the composition of the invention. However, e.g. a small amount of humidity, e.g. up to about 1 % water, may nevertheless be present, e.g. as an intrinsic impurity in some of the excipients used, or as part of the active ingredient when this is e.g. a hydrate, e.g. when crystal form A (see WO 99/01458) of pimecrolimus is used.

"%" herein means percent on a weight by weight (w/w) basis.

"Total weight of the composition" is to be understood as referring to the total weight including surfactant/emulgator, but without propellant gas.

A particularly beneficial aspect of the composition of the invention is that while the components of the above oily solvents are solubilizing agents, they additionally may possess penetration enhancing properties, thus contributing to keeping the formulation both simple and effective.

"Treatment" as used herein includes prevention, namely prophylactic as well as curative treatment.

The active agent component may be in free form or pharmaceutically acceptable salt form if such forms exist.

The invention thus provides a formulation for application to a body surface as a foam, comprising the active ingredient pimecrolimus and a foamable carrier vehicle as defined above. The active ingredient may be present as an integral part of the formulation, or some components may be held separately to other ingredients of the formulation and be combined therewith during formation of the foam. The formulation comprises a foaming agent (particularly, at least one surfactant/emulgator) which is capable of promoting production of a foam structure.

The invention therefore also provides a foamable carrier and an active ingredient with some components of the carrier packaged separately thereto, which are admixed with the other components during the foaming process.

The foam may be exposed to the atmosphere so that it dries into a coating, or may be covered by conventional dressings.

The composition of the invention is applied to the body site of interest in the form of a foam and it is therefore necessary that the composition undergoes a foaming process before application to the body. In the foaming process gas is forced into or is formed within the formulation to entrap small bubbles of gas therein, thereby forming the foam. Any suitable gas or gas producing system can be used to produce the foam, e.g. butane, propane and nitrous oxide, but other gases are also suitable. Normally the foam is produced by conventional means such as aerosol technology.

The composition may be stored in any convenient container until required. Generally, the container is designed to preserve the sterile nature of the formulation. The container will conveniently be provided with means to foam the composition when required.

The invention thus also provides a closed container containing a composition of the invention, capable of expelling the formulation in the form of a foam. For example, the container may be an aerosol canister, containing a pressurized gas which in use causes production of the foam. Alternatively, the gas may be produced by a chemical reaction when two different ingredients, contained in e.g. two portions of a sachet, are mixed together. The closed container may have separate reservoirs for the foamable carrier or parts thereof and the active ingredient. Thus the foamable carrier or parts thereof and the active ingredient are stored separately during storage and are admixed together in suitable proportions during the foaming process.

The invention also provides an apparatus to produce a foam for application to a body surface from a composition of the invention, comprising:

a) a closed container having a reservoir containing the foamable carrier or parts thereof, and a reservoir containing the active ingredient and the remaining parts of the carrier; and
b) means to produce a foam from the foamable carrier.

Optionally further foaming agents may be mixed with the foamable carrier.

The gel may be sterilised and this is generally desirable for medical use. Sterilisation may take place by autoclaving the composition, e.g. at temperatures of from about 100°C to about 125°C, e.g. for less than 30 minutes.

The advantages of applying a topical product in the form of a foam include:

- easy and rapid application;
- conformity to surface irregularities;
- insulation of the diseased area;
- cooling of the tissues;
- antibacterial action to prevent infection;
- biocompatibility with tissue; and/or
- maintenance of a moist environment.

The foam produced may subside over a period of time, e.g. 3 to 24 hours, as some of the gas entrapped in the foam structure escapes. The foamed composition gradually dries to produce a foam sheet which still retains a basic foam structure and which may cover the site to which the foam was applied. This foam sheet can be left in place as a protective cover.

The composition of the invention will normally be applied directly to the body site of interest in the form of a foam produced from a suitable device, such as an aerosol, immediately before administration. It is, however, possible to pre-produce an amount of the foamed composition which is then applied onto the body site by any suitable means, e.g. by hand or by spatula.

The composition of the invention may optionally comprise **further conventional excipients**, such as **plasticizers, humectants** (e.g. glycerol, propane-1,2-diol, polypropylene glycol and other polyhydric alcohols), **free radical scavengers, anti-oxidants, viscosity-adjusting agents, dyes** and **colorants**, e.g. as described in H.P. Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 5th Edition (2002).

The composition of the invention is indicated for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. The terms "skin" and "cutaneous" should be understood broadly as comprising also diseases of e.g. nail or mucosa. Examples of immunologically-mediated diseases include alopecia areata, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, and lupus erythematous. Examples of skin diseases include dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, acne, autoimmune diseases such as chronic rheumatoid arthritis, scleroderma and the like.

The invention further provides **a composition** as defined above **for use** in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

It further provides **a method for treating** inflammatory and hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases comprising administering a composition of the invention to a patient in need thereof.

Still further, it provides the **use** of a composition of the invention **in the preparation of a medicament** for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

It further provides the **use of a carrier vehicle** as defined above to enhance penetration of pimecrolimus into human skin, nail or mucosa.

The composition of the invention may be prepared in conventional manner by working up the components into a pharmaceutical composition. For example, the composition of the invention may be obtained by dissolving pimecrolimus in hexylene glycol and/or oleyl alcohol or medium chain triglycerides, and other components, e.g. dimethylisosorbide and the further excipients, may be added at the appropriate time as is conventional.

The following Examples illustrate the invention. The compounds are in free, i.e. neutral or base form unless specified otherwise.

Example 1: Foam

Component	Amount (g)
Pimecrolimus	1.0
1) Oily solvents:	
i) hexylene glycol	2.5
ii) oleyl alcohol	2.5
iii) dimethylisosorbide (Arlasolve^R)	77.2
medium chain triglycerides (oil)	10.0
2) Consistency agents:	
hydroxypropyl cellulose (Klucel MF)	0.5
stearyl alcohol	2.0
3) Preservative:	
Phenonip^R (a p-hydroxybenzoic acid ester with ethyleneglycol phenylether)	0.3
4) Surfactants/emulgators:	
glyceryl monostearate	2.0
Sisterna SP-30 and SP-70	1.0 (each)
(= non-ionic sugar esters, mild emulgators)	
	Total 100.0
5) Propellant:	
butane/propane 80/20	

The preparation is according to conventional manufacturing procedures for a foam.

Example 2: Foam

Component	Amount (g)
Pimecrolimus	1.0
1) Oily solvents:	
i) hexylene glycol	10.0
ii) medium chain triglycerides (oil)	59.7
2) Water	10.0
3) Consistency agents:	
polyvinylpyrrolidone (PVP K90)	2.0
stearyl alcohol	5.0
4) Preservative:	
Phenonip^{R} (a p-hydroxybenzoic acid ester with ethyleneglycol phenylether)	0.3
5) Surfactants/emulgators:	
glyceryl monostearate	2.0
lecithin	10.0
Total	100.0
6) Propellant:	
butane/propane 80/20	

The preparation is according to conventional manufacturing procedures for a foam.

Example 3: Foam

As for Example 2, whereby as solvent i) only 5.0 g hexylene glycol is used, and as solvent ii) 5.0 g dimethylisosorbide is included in addition to the triglycerides.

Claims:

1. A pharmaceutical foam composition substantially free of ethanol and comprising pimecrolimus in a carrier vehicle comprising a mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i) hexylene glycol;

ii) optionally oleyl alcohol; and

iii) dimethylisosorbide and/or medium chain triglycerides;

and additionally:

iv) when oleyl alcohol is absent, water in an amount of less than 25 %;

v) at least one consistency agent;

vi) at least one preservative; and

vii) at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients.

2. A composition according to claim 1 substantially free of ethanol and water and comprising pimecrolimus in a carrier vehicle comprising a 3-component mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i') hexylene glycol;

ii') oleyl alcohol; and

iii') dimethylisosorbide and medium chain triglycerides;

and additionally:

v') at least one consistency agent;

vi') at least one preservative; and

vii') at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients.

3. A composition according to claim 1 comprising pimecrolimus in a carrier vehicle comprising a 2-component mixture of oily solvents amounting to at least 40 % of the total weight of the composition and consisting of:

i") hexylene glycol; and

iii") dimethylisosorbide and/or medium chain triglycerides;

and additionally:

iv") water in an amount of less than 25 %;

v") at least one consistency agent;

vi") at least one preservative; and

vii") at least one surfactant/emulgator; and propellant gas for foaming;

and optionally further conventional excipients.

4. A composition according to claim 1 or 2 comprising pimecrolimus in a carrier vehicle consisting of:

i') hexylene glycol;

ii') oleyl alcohol; and

iii') dimethylisosorbide and medium chain triglycerides;

and additionally:

v') hydroxypropyl cellulose and/or stearyl alcohol;

vi') p-hydroxybenzoic acid ester with ethyleneglycol phenylether; and

vii') glyceryl monostearate and non-ionic sugar esters; and propellant gas for foaming.

5. A composition according to claim 1 or 3 comprising pimecrolimus in a carrier vehicle consisting of:

i") hexylene glycol; and

iii") medium chain triglycerides and optionally dimethylisosorbide;

and additionally:

iv") water in an amount of less than 25 %;

v") polyvinylpyrrolidone and stearyl alcohol;

vi") p-hydroxybenzoic acid ester with ethyleneglycol phenylether; and

vii") glyceryl monostearate and lecithin; and propellant gas for foaming.

6. A composition according to any one of claims 1 to 3 for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

7. A method for treating inflammatory and hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases comprising administering a composition according to any one of claims 1 to 3 to a patient in need thereof.

8. Use of a composition according to any one of claims 1 to 3 in the preparation of a medicament for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

9. Use of a carrier vehicle as defined in any one of claims 1 to 3 to enhance penetration of pimecrolimus into human skin, nail or mucosa.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 2004/016289 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; LEDERGERBER, DOROTHEA; SONNTAG, JEA) 26 February 2004 (2004-02-26) the whole document page 2, lines 8-30 page 3, lines 1-10 page 4, lines 11-22 page 7, lines 13,11-20 examples 6-9,12-15,16-1718-20,22-25 claims 1-3,6	1-9
Y	WO 02/080978 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; LEDER) 17 October 2002 (2002-10-17) page 2, paragraph 1-4; tables 1,2	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 2005	28/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Luangkhot, N

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2001/051650 A1 (KRIWET KATRIN ET AL) 13 December 2001 (2001-12-13) paragraphs '0047!, '0048!, '0050!, '0052! - '0054!, '0056! example 11	1
Y	US 2001/031769 A1 (JACKMAN MARTIN ET AL) 18 October 2001 (2001-10-18) paragraphs '0077!, '0083! - '0088! examples 1,2,8-11,20 paragraphs '0116!, '0124! claims 1-4,9	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/003669

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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